

Research progress on the genetic factors and treatment methods of gynecological malignant tumors

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Abstract:

Gynecological malignancies include a variety of types, such as CC, EC, and OC, and the degree of malignancy varies greatly among different types and patients. In addition, studies targeting gynecological malignancies have found that genetic alterations in pathways and gene mutations leading to abnormal cell proliferation can lead to the appearance of cancer. Further research is needed in this area to explore preventive measures to reduce the incidence in high-risk women. This article analyzes the genetic mechanism, environmental factors, symptoms, and treatment of gynecological malignancies. Although optimization of treatment has reduced cancer mortality, the malignancy of tumors remains high, and most patients are at risk of recurrence. Multiple genes related to the development of gynecological malignancies and the limitations of traditional treatment methods such as chemotherapy and radiotherapy were also mentioned, emphasizing the importance of research targeting genetic mechanisms in order to provide more accurate and personalized screening and prevention programs. This article highlights the important role of genetic factors in the occurrence of gynecological malignancies, especially EC and OC. It points out the relationship between some key genetic variants and gynecological cancers, which provides a reference for future research. In addition, the long-term efficacy and safety of emerging therapies such as targeted therapy and immunotherapy, which are not mentioned in this article, also exhibit large prospects and need to be further verified and explored.

Keywords: Gynecologic malignancies; gynecologic cancers; genetic factors.

1. Introduction

Gynecologic malignancies include many types, among which cervical cancer, endometrial cancer, and ovarian cancer are the most common. The malignant degree of gynecological malignant tumors shows great variety among different types and patients. In recent years, cancer mortality has been reduced due to the optimization of treatment methods. However, this does not mean that the degree of malignancy is reduced. The spite of cervical cancer and ovarian cancer has maintained a relatively high level in recent years [1]. Although the cure rate of early-stage cancers is high, most patients are still at risk of recurrence for cancers because of their well-differentiated level [2]. Gynecological malignancies have had a profound impact on society. These cancers affect women's health, increase the burden on the medical system, and require high-cost treatment and long-term care. In addition, these cancers are often found in the late stage, and the prognosis is poor, which brings psychological and economic pressure to patients and families.

Genetic studies of gynecologic malignancies have shown

that genetic factors play an important role in the incidence of such cancers. Especially ovarian cancer and endometrial cancer showed strong familial aggregation. Compared with mutant cancer, hereditary cancer is more likely to have female members of multiple generations in the family suffering from the same or related types of cancer [3].

The incidence of gynecologic malignancies is closely related to family history. The incidence of reproductive system-related cancers in families carrying disease-causing genes is much higher than that in families without disease-causing genes [4]. In recent years, the incidence of various gynecological tumors has shown an upward trend in society [3].

Many genes are associated with the development of gynecological malignancies. In recent studies on pathogenic genes, scholars found that PI3K/MAPK and TGF β Genomic changes in signaling pathways are likely to lead to cervical cancer, and TP53 gene mutations lead to abnormal cell proliferation, leading to ovarian cancer. Heritable BRCA1, BRCA2, p53, ATM, and other genes tend to increase the risk of gynecological malignant tumors [5]. These tumors, such as cervical cancer, endometrial can-

cer, ovarian cancer, malignant transformation of uterine fibroids, vaginal cancer, and vulvar cancer, generally have no obvious symptoms in the early stage. With the development of the disease, there will be abnormal irregular bleeding, such as vaginal bleeding, and postmenopausal bleeding, accompanied by back and leg pain, urination, and defecation problems [6, 7].

Traditional treatment methods such as chemotherapy and radiotherapy have been used for a long time in the treatment of gynecologic tumors. Still, we cannot ignore the side effects they have on the body. In order to seek more effective and safe treatment methods, new treatment methods such as targeted therapy and immunotherapy have become the focus of current research. However, the benefits of these new methods still need to be further verified and explored. Therefore, the study of the genetic mechanism of gynecologic tumors is particularly important. By deeply studying the genetic mechanism of gynecologic tumors, we can better understand the mechanism of disease occurrence and provide patients with more accurate and individualized screening and prevention programs. This will help identify patients' risks in advance and take corresponding preventive measures, thus minimizing the pain and recovery period of patients. Although considerable progress has been made in the study of gynecologic malignancies, there are still gaps in some fields. While the pathogenesis of common cancers such as cervical, endometrial, and ovarian cancers is well understood, further research is needed to explore how prevention measures can reduce the incidence of these cancers in high-risk women. Based on this, this article will provide some recommendations for prevention measures for people of different ages and different immune states and will provide advice for future research.

2. Underlying Mechanisms of Hereditary Gynecological Malignancies

2.1 Heritability of Gynecologic Malignancies

Gynecologic malignancies are associated with a variety of genetic cancer syndromes. Gene variants with high cancer susceptibility usually occur in hereditary cancer syndromes, and these variants follow an autosomal dominant inheritance pattern.

The pathogenesis of gynecologic tumors mainly involves the interaction of genetic factors and environmental factors. In particular, genetic susceptibility caused by specific gene variations has a significant impact on the risk of gynecological cancer.

The most common hereditary cancers include the following: First, BRCA1 and BRCA2-related hereditary cancer syndromes. Mutations in these two genes are associated

with a high risk of breast and ovarian cancer (OC). Second, Lynch syndrome (LS). It is caused by mutations in MLH1, MSH2, MSH6, and PMS2 genes and is mainly associated with endometrial cancer (EC). In addition, Peutz-Jeghers syndrome caused by STK11 gene mutation, although mainly associated with intestinal cancer, also increases the risk of gynecological cancer [8].

2.2 Common Gynecological Malignancies

2.2.1 EC

EC is the most common gynecological cancer in high-income countries, and the global incidence of it is increasing. The susceptibility caused by genetic factors is an important reason for this disease. The main nongenetic causes are the increasing obesity rate, the aging population, and fewer benign hysterectomies [6].

The diagnosis of early EC is usually due to the symptoms of postmenopausal bleeding. But it can also be diagnosed before menopause. For example, severe bleeding and continuous or intermenstrual bleeding are common symptoms before menopause.

The pathogenesis of EC mainly involves an imbalance in endocrine regulation, genetic factors, and lifestyle factors. This article mainly analyzes genetic factors.

In terms of Endocrinology, the proliferation and shedding of endometrium are significantly affected by estrogen and progesterone. Excessive estrogen promotes endometrial cell proliferation, while progesterone inhibits this proliferation. Activation of the PI3K-Akt-mTOR signaling pathway increases endometrial hyperplasia through direct and indirect pathways (the direct way, such as estrogen, and the indirect way, such as insulin-like growth factor-1).

Genetically, LS is the most common genetic predisposition. It involves pathological variants in mismatch repair (MMR) genes such as MLH1, MSH2, MSH6, and PMS2, which in turn increases the lifetime risk of many other cancers, including EC. Among 16 MMR mutation carriers detected in one study, the total prevalence of LS was 3.2%. Of these, 50% were MSH6 mutation carriers, 25% were MSH2 mutation carriers, and 12.5% were MLH1 and path_PMS2 mutation carriers [9].

In addition, obesity, metabolic, and reproductive factors are also important risk factors, and obesity is closely related to the increased risk of EC.

2.2.2 CC

Cervical cancer (CC) is one of the most common types of cancer in women worldwide. In recent years, CC incidence and mortality have steadily increased worldwide, even under CC screening programs.

Most early CC has no obvious symptoms. As the disease develops, some common symptoms that may occur in-

clude increased or smelly vaginal discharge, pain during sex, pelvic pain, blood in the urine, or abnormal vaginal bleeding.

Genetic factors play an important role in the occurrence and development of CC. Specific gene variation or abnormal expression is closely related to the increasing risk of CC. Studies have found that the expression patterns of some genetic markers in CC patients are different from those in healthy individuals, such as HPV DNA and E6/E7 mRNA, which are related to HPV infection and the carcinogenesis process [7].

HPV infection can cause genetic changes in cervical epithelial cells and then develop into CC. The pathogenesis of CC involves multiple stages, and the process from HPV infection to precancerous lesions and then to the formation of CC may last for several years. During this time, the genomic stability of cervical epithelial cells is impaired due to persistent HPV infection, forming precancerous lesions.

2.2.3 OC

OC is one of the most lethal cancers in the female reproductive system. The greatest risk factor for OC is family history, with OC due to genetic factors accounting for approximately 25% of all OCs [10].

Early symptoms of OC may not be that obvious, but later symptoms can include abdominal distension, rapid weight gain or loss, abdominal pain, and frequent urination.

The genetic mechanism of OC mainly involves the mutation of multiple genes, among which the mutations of BRCA1 and BRCA2 genes are the most common, accounting for about 40% of OC in women with a family history. In addition, approximately 6% of ovarian/fallopian tube / peritoneal cancers are caused by mutations in genes other than BRCA1 and BRCA2, including multiple genes related to the Fanconi anemia pathway or involved in homologous recombination. Genes such as RAD51C and rad51d are also associated with genetic susceptibility to OC [1, 10]. Studies have shown that although the risk of ovarian cancer susceptibility caused by RAD51C and rad51d fluctuates with age, the cumulative risk of them before the age of 80 reached 11% and 13% [11].

2.2.4 Other Gynecological Malignancies

Malignant transformation of uterine fibroids, vaginal cancer, and vulvar cancer are also members of the hereditary gynecological tumor family. They are the less common types compared to the three malignancies mentioned above.

The genetic mechanism of malignant transformation of uterine fibroids involves a variety of genetic and epigenetic changes. First, mutations in specific genes, such as med12, HMGA2, and FH genes. Changes in these genes

may lead to abnormalities in the cell cycle and tumor suppressor functions. Secondly, epigenetic mechanisms, including DNA methylation, histone modifications, changes in miRNAs, and increase, also play an important role in the occurrence and development of uterine fibroids. In addition, the emergence of familial uterine fibroids, such as HLRCC (hereditary leiomyoma and renal cell carcinoma syndrome), emphasizes the role of genetic factors in such tumors.

Vaginal and vulvar cancer are two rare malignant tumors. The pathogenesis of vaginal and vulvar cancer is not fully understood, but HPV infection is known to be associated with their pathogenesis. Certain genetic predictions may influence an individual's susceptibility to HPV and the risk of carcinogenesis after viral infection.

2.3 Differences in populations

Hereditary gynecologic malignancies are significantly different among different ethnic groups.

A higher proportion of black women had squamous cell carcinoma than adenocarcinoma. However, no difference was observed in the distribution of disease stages between white and non-white patients.

In addition, it has been shown that the proportion of locally advanced CC among Asian American women is higher than that among white women in the United States [12].

In the Pacific Northwest, a high proportion of cases of gynecologic cancer occur among American Indian or Alaska Native women.

These data suggest that racial factors may affect the occurrence and progression of gynecological malignancies, especially CC. Compared with white women, women of certain races, such as Asian American women and African American women, have a higher incidence of locally advanced CC. Further studies are needed to clarify the role of genetic and environmental factors.

3. Screening, Treatment, and Inhibitor Development of Gynecologic Malignancies

3.1 Screening

Gynecological cancer screening methods mainly include CC screening and OC screening. CC screening usually uses Pap test and HPV detection. These methods can help early detection of CC and precancerous lesions.

Screening for OC is more complicated because early OC is often asymptomatic, and there is no widely accepted effective routine screening method for OC. However, for high-risk individuals, if there is a family history of the disease, an ultrasound examination and CA-125 blood test can be used as screening tools.

There is no established procedure for EC screening, but an annual gynecological examination is recommended for high-risk groups, which may include transvaginal ultrasound, hysteroscopy, and endometrial biopsy. Emerging screening methods explore the use of urine cytology and genomic and proteomic markers for non-invasive detection.

In addition, for all gynecologic malignancies, recognition and reporting of early symptoms such as abnormal bleeding are important screening components for early cancer detection.

3.2 Treatment

The treatment of gynecological malignant tumors usually includes surgical resection, chemotherapy, radiotherapy, targeted therapy, and immunotherapy. The preferred treatment is the surgical removal of the tumor, especially in the early stages of cancer, where as many cancer cells as possible can be removed. Chemotherapy is usually performed with platinum-based and taxol-based regimens as maintenance therapy to prolong disease-free survival. Radiation therapy, targeted therapy, and immunotherapy may also be considered for gynecologic cancers that are recurrent or difficult to surgically remove.

The main treatments for EC are total hysterectomy and bilateral salpingo-oophorectomy. For premenopausal women presenting with early lesions, ovarian preservation may be considered to avoid the adverse consequences of surgical menopause without affecting survival. For intermediate and high-risk cases, adjuvant radiotherapy can reduce local recurrence.

OC is usually treated with surgical resection of the tumor and chemotherapy, especially maintenance therapy with platinum drugs and paclitaxel. In recent years, in view of the recurrence of patients, targeted therapy and immune therapy have been introduced. Examples include PARP inhibitors and the angiogenesis inhibitor bevacizumab [13]. In practical application, the choice of each treatment method depends on the type and stage of cancer, the health status of patients, and the feasibility of treatment.

3.3 Inhibitor Development

Inhibitors in gynecologic cancer therapy involve a variety of mechanisms, including hormone receptor inhibition, blockade of signaling pathways, and epigenetic regulation.

Among them, the development of CC inhibitors focuses on the molecular mechanisms that regulate cell proliferation and cycle progression and promote or inhibit tumor development. Studies have shown that MicrorRNA-29a inhibits cell proliferation and cell cycle by regulating p16 methylation, thereby fighting CC.

In addition, in the field of OC treatment, blockers (Immune checkpoint inhibitors, ICIS) as an immunotherapy means can restore the cytotoxic ability of T cells by targeting immune checkpoints such as CTLA-4, PD-1, and PD-L1 so as to attack cancer cells.

In terms of epigenetic regulation, epigenetic modulators such as 5 , -Aza-Cytidine slow down tumor growth through specific demethylation mechanisms, which points to a new therapeutic direction.

4. Conclusion

This article reviews the main types of gynecological malignant tumors (CC, EC, and OC). It emphasizes the important role of genetic factors in pathogenesis. The genetic mechanism and pathogenesis of several important hereditary cancer syndromes are also pointed out. This article also discusses the treatment of gynecological malignant tumors. Finally, Emphasizing the necessity for thorough exploration into the genetic intricacies of gynecological malignancies.

By delving deep into the genetic intricacies of gynecological malignancies, this paper aims to provide a comprehensive understanding of gynecological malignant tumors and provide patients with more accurate and personalized screening and prevention programs. By understanding the association of genetic variants associated with pathogenic pathways with cancer risk, high-risk individuals can be identified early. On this basis, corresponding preventive measures can be taken to reduce the incidence and shorten the suffering and recovery period of patients. In conclusion, this study is of great significance for improving the prevention and treatment of gynecological malignant tumors and reducing morbidity and mortality.

According to the research in this paper, suggestions for possible patients are as follows: Young women in their 20s should strengthen lifestyle management, maintain a healthy weight, and avoid smoking and excessive alcohol consumption. Women older than 30 years old, especially those with a family history of cancer inheritance, should receive genetic testing to assess cancer risk and regular gynecological examinations. High-risk people can consider drug or surgical prevention. All women should maintain a balanced diet and regular exercise to reduce the risk of cancer.

For the future research direction, the following suggestions are put forward:

First, considering the role of the PI3K/Akt/mTOR signaling pathway in endometrial cancer, the development of inhibitors specifically targeting each link of this pathway may have potential efficacy in the treatment of endometrial cancer.

Second, for the common TP53 gene mutations and BRCA gene family mutations in ovarian cancer, develop drugs that can promote the functional recovery of these genes or inhibit the tumor growth caused by mutations.

In addition, in view of the effectiveness of immunotherapy in some gynecological tumors, more molecular mechanisms and targets related to tumor immune escape, such as PD-L1, CTLA-4, etc., should be studied to develop new immunotherapy strategies.

Although this article provides recommendations on treatment, the long-term efficacy and safety of emerging treatment methods such as targeted therapy and immunotherapy need to be further verified and explored. Therefore, future research needs to pay more attention to how to reduce the incidence of gynecological malignancies through early screening and prevention strategies, and how to optimize existing treatment methods to reduce side effects and improve quality of life.

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